REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The specification has been amended to include representative amino acid sequences of H3, H4, H2A, H2B, H2A.X and H3.3. These sequences have been designated SEQ ID NOs:11-16, respectively. Applicants submit that these histone sequences were publicly available from the NHGRI/NCBI database (referenced at page 4, lines 23-25 of the application) at the priority date of the present application, and, therefore, their inclusion in the application does not add new matter. The relevant accession numbers are H3 histone - Accession no. 0710252A; H4 histone - Accession no. 0901261A; H2A histone - Accession no. AAN59974.1; H2B histone - Accession no. AAN06685.1; H2A.X histone - Accession no. NP_002096; and H3.3 histone - Accession no. CAA88778 --- the sequences presented as SEQ ID NOs:11-16 are the mature forms of the histones and thus do not include the N-terminal methionine residue, which is removed during post-translational processing. Therefore, the numbering of the specific residues (e.g., lysine residues) in these sequences corresponds to that in Tables 1 and 2.

The specification has also been amended to include the Sequence Listing submitted herewith on separate sheets. Applicants submit that entry of the Sequence Listing does not raise the issue of new matter. The computer readable copy of the Sequence Listing submitted herewith is the same as the attached paper copy of that Listing.

The claims have been revised to define the invention with additional clarity. Specifically, claims 1 and 20 have been amended to specify that the modified histone is acetylated at a lysine residue corresponding to position 16 of SEQ ID NO:12 (i.e., Lys 16 of H4) or methylated at a lysine residue corresponding to position 79 of SEQ ID NO:11 (i.e., Lys 79 of H3). These are the

specific histone modifications from Tables 1 and 2 that were elected in response to the species election requirement.

Claim 1 has also been amended to delete the term "said" before the first reference to "nucleosomes". Claim 7 has been amended so as to be drawn to a "method of assessing a disease condition in an individual". Basis for the revision is found on page 11, lines 12-21 of the application, in combination with the passage at page 13, lines 28-29, and page 23, lines 20-22. Claims 10, 11 and 48 have been amended to recite the histone modifications listed in Table 1 and/or 2. Claims 12 and 32 have been amended to correct typographical errors. Claims 4, 5, 15-19, 21-24, 34 and 36 have been deleted without prejudice.

The Examiner's objection to claim 23 is moot in view of the cancellation of that claim.

Claims 4, 5, 10, 11, 16-18, 21-24, 34, 36 and 48 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is in order in view of the above-noted claim revisions and comments that follow.

As pointed out above, representative amino acid sequences of histones H3, H4, H2A, H2B, H2A.X and H3.3 have been included in the application as SEQ ID NOs:11-16, respectively, and the amended claims refer to a specified type of modification at a particular amino acid residue corresponding to a specified position of the referenced SEQ ID NO.

Claims 18 and 21 have been cancelled, thus rendering moot the Examiner's rejection of these claims.

Reconsideration is requested.

Claims 1-36 and 44-48 stand rejected under 35 USC 103 as allegedly being obvious over Allis et al (US 2006/0073517) in view of Allis (b) (US 2005/0069931). Withdrawal of the rejection is submitted to be in order for the reasons that follow.

Claims 1-6 and 20-25 (claims 4, 5 and 21-24 now being cancelled)

These claims have been revised so as to be drawn to the two specific histone modifications elected in response to the species election requirement. Although these two modifications are alluded to in Allis et al (see paragraphs [0072] and [0075]), this document does not provide any indication that these two specific histone modifications are associated with disease. Instead, Allis et al merely indicates that specific histone modifications, such as those recited in claims 1 and 20, can provide information relating to the control of gene expression in yeast. For example, Allis et al refers to the loss of silencing seen in yeast mutants of H3 Lys 79 (see paragraph [0072]), and the structure of the bromodomain of Gen5 bound to H4 Lys 16 acetyl-mark (see paragraph [0075]). Neither of these passages would have suggested to one skilled in the art that detection of methylation (in the case of H3 Lys 79) or acetylation (in the case of H4 Lys 16) at these specific residues could be used to assess a disease condition in an individual (see claims 1-6), for example cancer (see claims 20-25). Therefore, claims 1-6 and claims 20-25 would not have been obvious over Allis et al.

Furthermore, there is no mention of either of these two specific histone positions in Allis (b). Thus, there is nothing in the disclosure of Allis (b) that would have indicated to the skilled person that detection of the two specific histone modifications recited in claims 1 and 20 would be useful for the detection of disease conditions, such as cancer. Thus, the subject mater of claims 1-6 and 20-25 would not have been obvious over Allis et al taken in combination with Allis (b).

Claims 7-14

Independent claim 7 as now presented is directed to a method of assessing a disease condition in an individual using a double-antibody format, such that one antibody binds to a nucleosome, while the other antibody binds specifically to a modified histone.

Neither Allis et al nor Allis (b) teaches or would have suggested the use of such a two-site immunoassay for the detection of modified histones, and such assays had not been described for the detection of modified histones as of the priority date of the application. Methods involving two-site immunoassays were known in the art for the detection of other protein molecules in liquid media, such as blood. However, if it had been obvious that such a method could be used to detect modified histones, Applicants submit that the authors of Allis et al and Allis (b) would have mentioned it.

The development of a two-site immunoassay to detect modified histones is problematic since, although a first antibody may be designed to bind to a first epitope containing the histone modification, it would not have been at all apparent as to what epitope a second antibody would bind, especially as the same epitope cannot be used for the both the immunoextraction antibody and the labelled antibody epitope sites. If the second epitope were on the same histone, there would be a risk of masking in the intact nucleosome, whereas if it were on an intact nucleosome (e.g., directed to bind a nucleosome-DNA complex epitope) this epitope would not exist if the nucleosomes were degraded in blood.

The Examples of the present application report for the first time the use of a two-site immunoassay for the detection of modified histones, namely a two-site ELISA assay in which the first antibody is directed to nucleosomes (of no particular modification), and a second

antibody is used to detect histone modifications on the immune-extracted nucleosomes. This assay was able to detect histone modifications associated with cancer.

As explained above, such a two-site immunoassay is particularly suited to detection of protein molecules in liquid media, e.g., biological fluids, as recited in claim 7. Furthermore, such assays are much more analytically sensitive (by several orders of magnitude) and specific than single antibody methods, faster and simpler to perform and simple to adapt for automated instrumentation.

There is nothing in either Allis et al or Allis (b) that would have suggested to one of ordinary skill in the art that such methods could be used to detect modified histones. In particular, an artisan would not have found any guidance in the cited art as to the identity of the second epitope, the choice of which would not have been obvious for the reasons explained above.

Thus, the two-site antibody method of claims 7-14 would not have been obvious over Allis et al and Allis (b), alone or in combination.

Claims 26-35 (claim 34 now being cancelled)

These claims are dependent on the methods of claims 1-25, and, therefore, would not have been obvious over the cited art for the reasons discussed above.

Claims 44-48

These claims relate to a method of determining the presence of a cell-free nucleosome having a histone modification by detecting the presence of an endogenous antibody which binds specifically to that particular histone modification.

Although Allis et al and Allis (b) describe the use of antibodies to detect specific histone modifications, neither of these documents mentions the possibility of detecting endogenous

antibodies that bind specifically to histone modifications, as set out in claim 44. In fact, at the priority date of the application, one of ordinary skill in the art would not have even known that such endogenous antibodies existed. Therefore, such a method would not have been obvious over the cited documents.

In view of the above, it will be clear that withdrawal of the rejection of the claim as obvious is in order and the same is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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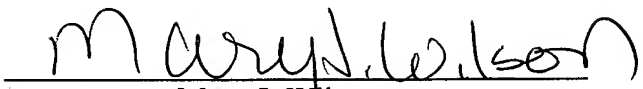
By: 

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